Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 166, 168, 170, 177 and 247 are pending in the application, with claim 166 being the independent claim. Claim 170 has been amended. Support for the amendment to claim 170 can be found at page 52, lines 28-32. Claim 247 has been added. Support for claim 247 can be found throughout section IV.K.2 of the application on pages 52-54 and in particular at page 52, line 14 and page 54, line 19. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Provisional Double Patenting Rejection

The Examiner has provisionally rejected claims 166, 168, 170 and 177 under the judicially created doctrine of obviousness-type double patenting over claims 1-29 of copending Appl. No. 10/031,345. (Office Action, page 2.)

Applicants note that, according to § 804(I)(B) of the Manual of Patent Examining Procedure (M.P.E.P.), when provisional double patenting issues are raised in copending applications, "[i]f the 'provisional' double patenting rejections in both applications are the only rejections remaining in those applications, the examiner should then withdraw that rejection in one of the applications (e.g., the application with the earlier filing date) and permit the application to issue as a patent. The examiner should maintain the double

patenting rejection in the other application as a 'provisional' double patenting rejection which will be converted into a double patenting rejection when the one application issues as a patent."

As noted by the Examiner, Applicants will appropriately address the double patenting rejection at a later date, in the event it is converted to an actual double patenting rejection pursuant to MPEP § 804(I)(B). (*See id.*)

Rejections under 35 U.S.C. § 102

The Examiner has rejected claim 170 under 35 U.S.C. § 102(e) as allegedly being anticipated by Chien *et al.* (U.S. Patent No. 6,150,087) ("Chien"). (Office Action, page 3.) Applicants respectfully disagree. However, in order to expedite prosecution, Applicants have amended claim 170, as noted above, so that claim 170 recites a CTL/HTL epitope conjugate, wherein the CTL epitope of the CTL/HTL epitope conjugate is the isolated peptide of claim 166, wherein the CTL epitope is linked to a non- HCV(Hepatitis C Virus) HTL epitope, wherein the CTL epitope is linked to the non- HCV HTL epitope either directly or via a spacer at the amino or carboxy terminus of the CTL peptide, and wherein the spacer is no more than six residues in length.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987); *see also* MPEP § 2131. As stated by the Examiner, "Chien et al. do not teach the peptide of claim 166/168." (Office Action, page 4). Chien merely discloses a peptide sequence 50 amino acids in length (AA1850-AA1900) which *comprises* the sequence GVAGALVAFK.

(*See* Chien, col. 27, second paragraph). Applicants note that "although . . . specific claims are subsumed in [a prior art reference's] generalized disclosure . . ., this is not literal identity." *Minnesota Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.*, 24 USPQ2d 1321, 1332 (Fed. Cir. 1992). None of the peptides disclosed in Chien corresponds exactly to Applicants' claimed peptide. Therefore, Chien fails to teach every aspect of the claimed invention. Applicants assert that claim 170 is clearly not anticipated by Chien.

In addition, currently amended claim 170 recites a CTL/HTL epitope conjugate wherein the CTL epitope is linked to a **non**- HCV HTL epitope either directly or via a spacer at the amino or carboxy terminus of the CTL peptide, wherein the spacer is no more than six residues in length. Chien discloses a 50 amino acid HCV peptide which does not contain any non-HCV sequence. The Examiner has alleged that Chien also teaches this 50 amino acid HCV peptide conjugated to tetanus toxoid wherein tetanus toxoid inherently contains HTL epitope(s). (Office Action, page 3.) However, Applicants' submit that Chien does not teach or suggest Applicants' invention as recited in amended claim 170. Amended claim 170 requires that the peptide of claim 166 is linked to a non- HCV sequence either directly or via a spacer, wherein the spacer is no more than six residues in length. As stated above, Chien does not teach the exact peptide sequence of Applicants' invention. Furthermore, Chien neither teaches an epitope conjugate in which the CTL epitope of Applicants' invention is linked directly to a non-HCV HTL epitope nor teaches an epitope conjugate in which the CTL epitope of the Applicants' invention is linked to a non-HCV HTL epitope via a spacer, wherein the

spacer is no more than six residues in length. Therefore, Chien does not disclose every element of currently amended claim 170.

In addition, new claim 247 depends from claim 170 and therefore contains each and every limitation of claim 170. As a result, claim 247 is not anticipated by Chien.

Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 103

The Examiner has maintained the rejection of claims 166, 168, 170 and 177 under 35 U.S.C. § 103(a) as allegedly being obvious over Chien in view of Berzofsky *et al.*, U.S. Patent No. 5,980,899 ("Berzofsky"), and in view of Guo *et al.*, *Nature* 360: 364-366 (1992) ("Guo"). (Office Action, page 4.) Applicants respectfully disagree and traverse the rejection.

I. The Examiner has improperly relied upon an inherency argument.

Applicants assert that the Examiner has improperly relied on the unexpected properties of the claimed peptide *identified by the Applicants* in the obviousness analysis. Obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. *In re Rijckaert*, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993). The Examiner extends this improper analysis by arguing that "the functional attributes of [Applicants' claimed peptide] would presumably be present in the peptide of Chien et al. in that said larger peptide would be processed in vivo." (Office Action, page 7.) The Examiner, however, has not provided any evidence to support this assertion, nor does the Examiner show that Chien has any teaching of the unexpected properties previously presented in Applicants' reply of August 29, 2006. (*See*

for example, page 11 of the Applicants' response describing the strong CTL-inducing response of the Applicants' peptide.) Even assuming that the larger peptide of Chien would be processed *in vivo* to produce Applicants' claimed peptide (which it would not necessarily do as described further below), the Examiner is improperly relying on the finding of unexpected functional attributes of the claimed peptide *identified by the Applicants* to use Chien in combination with Berzofsky and Guo, in an obviousness rejection.

The Examiner also has stated that "there is no evidence of record that suggests that the peptide taught by Chien et al. contains another immunodominant epitope that would suppress the response to the peptide recited in the claims." (Office Action, page 7.) Applicants note that the discussion of immunodominant epitopes was presented to describe what was known by one of ordinary skill in the art at the time the invention was filed. In particular, the teaching of Yewdell & Bennick (*Annu. Rev. Immunol.* 17:51-88 (1999)) suggests that it is difficult to identify exactly which specific peptides are capable of inducing an immune response within a given longer sequence because one of ordinary skill in the art would know that longer sequences often do contain immunodominant epitopes. Thus, the Yewdell reference supports the argument that the identification of Applicants' particular peptide is nonobvious over Chien in view of Berzofsky and/or Guo. Furthermore, the Examiner is again relying on the unexpected functional attributes of the claimed peptide *identified by the Applicants* to support the obviousness argument. As noted above, however, it is improper to do so as obviousness cannot be predicated on what is not known at the time an invention is made. As described above, the unexpected

functional attributes of Applicants' claimed peptide was not known or described by Chien, Berzofsky and/or Guo.

The Examiner also makes the assumption that "if the peptide recited in the claims is an actual physiologically relevant CTL epitope than the larger molecule containing said epitope must be processed in vivo to result in said peptide." (Office Action, page 7.) The Examiner, however, has not presented any evidence to support that the fifty amino acid peptide itself would actually be present in a host, and furthermore has not disclosed any evidence that this particular fifty amino acid molecule would actually be properly processed *in vivo*. In fact, the Examiner states that "[t]here is no evidence of record that addresses the effect of the flanking sequences found in the peptide disclosed by Chien et al." (Office Action, page 7.) Applicants assert, as described below, that it is not their burden to produce this evidence.

Eisenlohr *et al.* (*J.Exp.Med.* 175:481-487 (1992) (of record as document AS6, IDS, filed March 18, 2004) was presented by the Applicants to support their argument that the identification of their claimed peptide was unexpected. More specifically, as noted in Applicants' Reply filed August 29, 2005, flanking residues can influence epitope processing. *See* Eisenlohr, Abstract. The Examiner states that the Eisenlohr reference "teaches that flanking sequences can also positively effect the presentation of an immunogenic peptide." (Office Action, page 7.) Applicants emphasize, however, that while flanking resides *may* be able to positively affect the presentation of an immunogenic peptide, that Eisenlohr also teaches that the addition of flanking residues can also destroy the antigenicity of a particular peptide. *See* Eishelohr, page 485, first paragraph. Therefore, an epitope embedded within a larger sequence may be processed

differently, and thus have different immunogenicity than the same epitope free of flanking or surrounding amino acid residues. In view of Eisenlohr, the Examiner cannot simply assume that the longer 50 amino acid peptide in Chien must be processed *in vivo* to generate Applicants' claimed peptide. Again, even assuming that the longer peptide would be processed *in vivo* to produce Applicants' claimed peptide, the Examiner cannot rely on the unexpected property identified by the Applicants, in the obviousness analysis.

The Examiner also looks at what is disclosed in the Applicants' application regarding peptide length noting that "the specification discloses that the peptide can be 30 amino acids long . . ." Applicants note that an obviousness analysis requires a comparison between the differences between the prior art and the *claimed* invention.

Thus, as discussed above, the Examiner's obviousness analysis cannot rely on the unexpected property of the claimed peptide identified by the Applicants. As discussed below, Applicants assert that, when the proper criteria in an obviousness analysis are considered, that the Examiner has not established a *prima facie* case of obviousness.

II. The Examiner has not established a prima facie case of obviousness.

As described above, in an obviousness analysis, it is improper to rely on the inherency of a certain feature. In order to establish a *prima facie* case of obviousness, the proper analysis is to first consider whether the following three criteria are met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation

of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP § 2143. Furthermore, without a motivation to combine, a rejection based on a *prima facie* case of obviousness is improper. *See In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998).

Applicants again assert that there is no suggestion or motivation to combine the reference teachings, and thus the first criteria necessary to establish a *prima facie* case of obviousness has not been met.

Applicants again note that currently pending claims 166, 168, 170, 177 and 247 are directed to an isolated peptide selected from a group which includes Applicants' elected peptide GVAGALVAFK. Chien, as discussed above, does not teach or suggest every element of Applicants' claimed invention. This is supported by the Examiner's own statement that "Chien et al. do not teach the peptide of claim 166/168." (Office Action, page 4.)

The Examiner has alleged that Chien in view of Berzofsky renders claims 166, 168, 170 and 177 obvious. (Office Action, page 4.) As noted previously, the Berzofsky article focuses on the NS5 region; the only exemplification in Berzofsky is with regard to the identification of a particular peptide within the NS5 region. *See* Berzofsky, Examples 1-4. The preferred peptides of Berzofsky, as listed in Fig. 1A, all correspond to peptides of the NS5 region. Berzofsky, Fig. 1A.

While Berzofsky generally describes other regions of HCV, it does not provide any teaching or guidance with regard to which specific regions of the HCV genome necessarily contain good targets for CTL, nor does it contain any teaching or guidance to identify Applicants' claimed peptide. Applicants' elected peptide, GVAGALVAFK, is

neither discussed, nor described in Berzofsky. In addition, the peptides of Applicants' claimed invention are determined using techniques which do not rely on the amphipathicity algorithm of Berzofsky. Berzofsky does not teach, or even suggest the techniques Applicants' utilized to identify candidate CTL epitopes. Given the relatively large number of possible epitopes that could be identified within the HCV genome, the Berzofsky article, without more, would not be viewed by one of skill in the art to teach or suggest Applicants' claimed invention. As such, Chien in view of Berzofsky does not render claims 166, 168, 170 and 177 obvious.

The Examiner has also alleged that Chien, in view of Berzofsky, and further in view of Guo allegedly renders claims 166, 168, 170 and 177 obvious. (Office Action, page 5.) Guo generally describes how CTL recognize viral peptides complexed with MHC and that these peptides generally are 9 to 11 amino acids in length. Guo, page 364. While Guo discloses peptide sequences from several proteins including ribosomal 60S, human Hsp70, and influence NP (Guo, Table 1), Guo does not contain any discussion regarding the identification of CTL epitopes within the HCV genome, nor does Guo disclose Applicants' elected peptide.

Accordingly, Chien, in view of Berzofsky, and further in view of Guo provide no motivation or suggestion to combine references, nor do they teach or suggest all of the claim limitations. At best, Berzofsky and/or Guo provide an invitation to experiment.

Thus, Applicants assert that the criteria requiring that a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify Chien or to combine reference teachings, has not been met. Therefore, a *prima facie* case of obviousness, with respect to claims 166, 168, 170

and 177, has not been established. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be reconsidered and withdrawn.

II. Even assuming that a *prima facie* case of obviousness has been established, Applicants assert that this *prima facie* case of obviousness can be rebutted.

Assuming, *arguendo*, that the Examiner has established a *prima facie* case of obviousness, Applicants assert that the *prima facie* case of obviousness can be rebutted. Rebuttal evidence may consist of a showing that the claimed compound possesses unexpected properties. *Dillon*, 919 F. 2d at 692-93. Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut *prima facie* obviousness. MPEP § 716.02; *see In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987). Applicants emphasize that the unexpected property of Applicants' claimed peptide is sufficient to rebut a *prima facie* case of obviousness. As discussed in detail above, the unexpected property of Applicants' claimed peptide cannot be relied upon by the Examiner to establish the *prima facie* case of obviousness itself.

As discussed previously in the Amendment and Reply filed November 29, 2004, Table XXIII ("Immunogenicity of identified supermotif-bearing peptides") shows that Applicants' elected peptide GVAGALVAFK exhibits the strongest CTL-inducing response in transgenic mice as compared to any of the other peptides listed in Table XXIII and compared to any of the other peptides which share the same A3 motif. Applicants also point out that in Table XVI, Applicants' elected peptide

GVAGALVAFK exhibits one of the strongest binding affinities as compared to over 400 other peptides which share the same A3 motif.

Thus, the CTL-inducing and binding characteristics of the GVAGALVAFK peptide, as determined by Applicants, demonstrate that the GVAGALVAFK has unexpected properties. In view of the improved binding properties of GVAGALVAFK as compared to over 400 other peptides sharing the same motif, and in view of the significantly greater CTL induction generated as compared to other peptides sharing the same motif, Applicants assert that this evidence of unobvious or unexpected advantageous properties is present and is sufficient to rebut a *prima facie* case of obviousness. It is the functional characteristic of the peptide, as determined by the Applicants, which renders the peptide to have an unexpected property, and thus renders the peptide non-obvious in view of the prior art. A showing of nonobviousness does not require that these features necessarily need to be present as limitations of the claims.

Based on the above, Applicants assert that even assuming a *prima facie* case of obviousness has been established, a *prima facie* case of obviousness can be rebutted using the evidence described above.

Other Matters

Applicants thank the Examiner for withdrawing the rejection of claim 170 under 35 U.S.C. § 112, second paragraph.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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